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Hormone-binding proteins and their associated hormones in patients with nephrotic syndrome

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Abstract
Aim: In the current study, we aimed to evaluate SHBG and TBG levels and their related hormone levels in patients with nephrotic syndrome and the control group.
Material and Methods: The current study was conducted at Istanbul University Cerrahpaşa Faculty of Medicine, Department of Internal Medicine, with a total of 33 patients and 11 healthy controls. The study groups were divided into 3 groups: normal serum creatine level, high serum creatine level and control group. SHBG, TBG, T3, T4, fT3, fT4, TSH, testosterone, free testosterone, prolactin, FSH, and LH levels were determined in all groups. Proteinuria, hypoalbuminemia, and hyperlipidemia were present in the patient groups.
Results: The mean age was 31.0 ± 11.0 years (Group 1), and 46 ± 15 years (Group 2) in patients with nephrotic syndrome. In the control group, the mean age was 29.0 ± 7.0 years. TBG, T3, T4, fT3, fT4 and TSH levels were found to be lower in the patient groups than in the control group. No statistically significant correlation was detected between SHBG and TGB and albumin, globulin and proteinuria, which are indicators of nephrotic syndrome.
Discussion: Nephrotic syndrome has important effects on the metabolism and regulation of protein or protein-protein-bound hormones and prohormones. This study indicates that individuals with nephrotic syndrome experience notable changes in SHBG, TBG, and related hormones. It can be said that this situation occurs as a result of the loss of both hormones and the proteins that bind these hormones from the kidneys.

Keywords
Nephrotic Syndrome, Hormones, Hormone Binding Proteins

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Introduction

Nephrotic syndrome is a kidney disorder characterized by a group of symptoms that result from damage to the small blood vessels in the kidneys [1]. The primary components of nephrotic syndrome include proteinuria, hypoalbuminemia, edema and hyperlipidemia [2]. The causes of nephrotic syndrome can vary, and it can be primary (idiopathic) or secondary to other underlying conditions [3]. Common primary causes include minimal change disease, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy [4]. Symptoms of nephrotic syndrome may include swelling, especially in the legs and around the eyes, fatigue, foamy urine (due to excess protein), and susceptibility to infections [5]. Oxidative stress (OS) results from a disparity between the generation and buildup of reactive oxygen species (ROS) within cells and tissues, and the capacity of a biological system to effectively eliminate these reactive byproducts [6,7]. OS plays an important role in the pathophysiology of various diseases, including nephrotic syndrome [8-14]. Management of OS in nephrotic syndrome may involve strategies to enhance antioxidant defenses. This can include dietary measures (such as increasing intake of antioxidant-rich foods), supplementation with antioxidants, and addressing underlying causes of oxidative stress, such as inflammation.

Diagnosis involves a combination of clinical evaluation, laboratory tests (such as urine and blood tests), and sometimes a kidney biopsy to determine the underlying cause and guide treatment [15]. Treatment aims to manage the underlying cause, control symptoms, and prevent complications. Medications such as corticosteroids, immunosuppressants, and diuretics may be prescribed, depending on the specific cause of nephrotic syndrome. It's essential for individuals with nephrotic syndrome to receive ongoing medical care and monitoring to manage the condition effectively. Sex hormone binding globulin (SHBG) is a beta globulin that binds testosterone with a uniquely high affinity and limited capacity [16]. SHBG is produced in the liver and, together with albumin, binds 97-99% of circulating testosterone. The primary function of SGBH is to regulate serum-free testosterone concentration. SHBG has the task of adjusting the blood level of free hormone against the fluctuating release of sex hormones [17]. The transport system of thyroid hormones in humans is carried out through a group of serum transport proteins that show different concentrations, thyroid hormone activity and distribution rates [18]. Thyroxin-binding globulin (TBG) is an unstable molecule with a molecular weight of 54 kilodaltons and is a member of the serine protease inhibitor family [19]. TBG is a minor component of alpha globulins and accounts for 70% of T3 and T4 in human sera. In this study, we aimed to evaluate SHBG and TBG levels and their related hormone levels in patients with nephrotic syndrome and the control group.

Material and Methods

In this study, serum SHBG and TBG-related hormone levels were compared in 33 patients with nephrotic syndrome and 11 healthy individuals who were followed up in the Department of Internal Medicine of Istanbul University Cerrahpasa Faculty of Medicine Hospital between 1999-2001. In the present study, the patient group was divided into two groups. The first group consisted of 20 patients whose ages ranged from 18 to 58 years and whose serum creatinine levels were within normal limits. The second group consisted of 13 patients whose ages ranged from 22 to 72 years and whose serum creatinine levels were high. The control group consisted of 11 healthy individuals aged between 22-48 years. Proteinuria, hypoalbuminemia, and hyperlipidemia were present in the patient groups. Serum SHBG, TBG, T3, T4, fT3, fT4 TSH, testosterone, free testosterone, prolactin, FSH, LH and E2 levels were measured in the patient groups and the control group. The data obtained as a result of the study was analyzed using the SPSS program.

Statistical Analysis

The statistical analysis of the obtained data was analyzed using the SPSS program. $P<0.05$ was considered statistically significant. Parameters in the study groups were expressed as mean and standard deviation. Mann-Whitney U test was used to compare study groups. ANOVA (Dunnet multiple comparison test) was used to compare the study group and control groups. The correlation between the parameters was checked with the Spearman correlation test. Multiple regression analysis was used to investigate the effects of albumin, globulin, proteinuria and creatinine on the changes in SHBG and TGB.

Ethical Approval

The study was conducted in accordance with ethical rules.

Results

The mean age was 31.0 ± 11.0 years (Group 1), and 46± 15 years (Group 2) in patients with nephrotic syndrome. In the control group, the mean age was 29.0 ± 7.0 years. The values of the parameters examined in the patient and control groups are shown in Table 1. TBG, T3, T4, fT3, fT4 and TSH levels were found to be lower in the patient groups than in the control group (Table 1). A notable statistical difference exists between Group

Table 1. Parameters of the study and control groups.

Parametre	Group 1 (n=20)	Group 2 (n=13)	Control (n=11)
Age (years)	31±11	46±15	29±7
T. Protein (mg/dL)	5.5±1.1	5.9±1.3	7.9±0.4
Albumin(mg/dL)	2.6±0.9	2.7±1.0	4.4±0.3
Globülin (mg/dL)	2.8±0.6	3.2±0.6	3.3±0.6
Proteinuri(gr/day)	6.3±1.6	4.7±1.2	0.0
TBG	11.8±2.9	18.4±19.2	20.0±4.6
T3	52.2±48.2	62.3±31.2	110.5±41.4
fT3	2.9±0.6	2.5±1.0	3.3±0.3
T4	5.1±2.8	6.4±2.4	6.7±2.1
fT4	1.1±0.3	0.9±0.2	1.2±0.1
TSH	1.6±0.9	2.5±1.7	2.5±0.4
SHBG	49.1±34.0	45.6±39.3	39.5±16.3
Testosteron	201.9±202.8	273.2±172.1	274.7±303.1
f Testosteron	10.3±7.5	10.1±3.3	7.7±7.6
Prolactin	9.3±3.7	13.8±6.3	10.5±5.1
FSH	3.8±3.9	5.0±3.3	4.5±3.2
LH	4.0±2.6	5.7±3.8	5.3±3.3
E2	0.8±2.6	9.1±21.3	13.0±22.3

Group 1: Patient with normal creatinine level; Group 2: Patient with high creatinine level; Group 3: Control

Table 2. Comparison of serum protein and hormone levels of nephrotic syndrome patient groups with control group.

Parametre	Group 1 (n=20)	Control (n=11)	p	Group 2 (n=13)	Control (n=11)	p
T. Protein (mg/dL)	5.5±1.1	7.9±0.4	<0.001	5.9±1.3	7.9±0.4	<0.001
Albumin(mg/dL)	2.6±0.9	4.4±0.3	<0.001	2.7±1.0	4.4±0.3	<0.001
Globülin (mg/dL)	2.8±0.6	3.3±0.6	0.067	3.2±0.6	3.3±0.6	0.807
TBG	11.8±2.9	20.0±4.6	0.089	18.4±19.2	20.0±4.6	0.913
T3	52.2±48.2	110.5±41.4	0.001	62.3±31.2	110.5±41.4	0.015
fT3	2.9±0.6	3.3±0.3	0.247	2.5±1.0	3.3±0.3	0.024
T4	5.1±2.8	6.7±2.1	0.164	6.4±2.4	6.7±2.1	0.932
fT4	1.1±0.3	1.2±0.1	0.851	0.9±0.2	1.2±0.1	0.049
TSH	1.6±0.9	2.5±0.4	0.101	2.5±1.7	2.5±0.4	0.995
Testosteron	201.9±202.8	274.7±303.1	0.582	273.2±172.1	274.7±303.1	1.0
f Testosteron	10.3±7.5	7.7±7.6	0.451	10.1±3.3	7.7±7.6	0.565
Prolactin	9.3±3.7	10.5±5.1	0.739	13.8±6.3	10.5±5.1	0.181
FSH	3.8±3.9	4.5±3.2	0.823	5.0±3.3	4.5±3.2	0.908
LH	4.0±2.6	5.3±3.3	0.421	5.7±3.8	5.3±3.3	0.944
E2	0.8±2.6	13.0±22.3	0.086	9.1±21.3	13.0±22.3	0.774

Table 3. Correlation analysis of laboratory parameters in patients with nephrotic syndrome

Variables		Albumin	Globulin	Proteinuria	SHBG	TBG
SHBG	r	0.121	0.221	-0.109		
	p	0.504	0.217	0.548		
TBG	r	0.250	0.080	-0.010	-0.275	
	p	0.161	0.659	0.958	0.121	
T3	r	0.195	-0.056	-0.166	0.086	0.182
	p	0.278	0.755	0.357	0.633	0.311
f-T3	r	0.286	-0.118	0.117	-0.259	0.080
	p	0.107	0.515	0.518	0.145	0.660
T4	r	0.497	0.187	-0.257	0.094	0.343
	p	0.003	0.299	0.149	0.604	0.050
f-T4	r	0.189	-0.256	0.229	0.026	-0.085
	p	0.292	0.150	0.200	0.885	0.637
TSH	r	-0.240	-0.126	-0.283	-0.262	-0.077
	p	0.178	0.485	0.110	0.142	0.671
Testosteron	r	0.184	0.066	-0.142	0.089	0.180
	p	0.306	0.716	0.430	0.621	0.317
f-testosteron	r	0.345	-0.176	-0.118	-0.140	-0.035
	p	0.049	0.329	0.512	0.437	0.847
Prolactin	r	-0.066	-0.139	-0.540	0.119	0.030
	p	0.717	0.439	0.001	0.511	0.870
FSH	r	0.102	-0.068	-0.345	-0.022	0.058
	p	0.572	0.708	0.049	0.904	0.749
LH	r	0.215	-0.105	-0.057	0.229	0.453
	p	0.230	0.562	0.753	0.200	0.008
E2	r	0.332	0.256	-0.119	-0.057	0.676
	p	0.059	0.150	0.511	0.751	0.001

1 and the control group in terms of T. Protein, Albumin and T3 (p<0.001). A statistically significant difference was detected in terms of T.Protein, Albumin, T3, fT3 and fT4 parameters in Group 2 and the control group. (p<0.05). In addition, no statistically significant difference was detected between Group 2 and the control group in terms of FSH and LH, E2, prolactin and TBG parameters (p>0.05) (Table 2). No statistically significant correlation was detected between SHBG and TGB and albumin, globulin and proteinuria, which are indicators of nephrotic syndrome. On the other hand, a significant correlation was detected between T4 and testosterone and albumin. (p=0.003, p=0.049). In addition, a significant correlation was detected between prolactin and FSH and proteinuria. (p=0.001, p=0.049). A significant correlation was detected between T4 and TBG (p<0.05). (Table 3).

Discussion

It is known that the main pathology in nephrotic syndrome is proteinuria , which results from the change in the permeability of the glomerular basement membrane. Almost all of the other components and metabolic complications of nephrotic syndrome develop due to urinary protein loss. Nephrotic syndrome has important effects on the metabolism and regulation of protein or protein-protein-bound hormones and prohormones. Although the loss of thyroxine-binding globulin in the urine and the resulting changes in thyroid functions in nephrotic syndrome are well known, there is no consensus on the changes in SHBG and other sex hormones and their mechanisms. There are many studies showing a decrease in the levels of serum TBG and related hormones in nephrotic syndrome, as well as a loss of TBG and related hormones in the urine.

In the study conducted by Ito et al. [20] in children with nephrotic syndrome who were untreated and had normal creatinine levels, they investigated TBG, T3, and T4 levels before treatment and in the remission period and found massive urinary TBG, T3, and T4 levels in the pre-treatment period compared to the remission period. They showed that there was a loss of fT3 and fT4. In addition, it has been determined that there is a positive correlation between urinary TBG excretion and proteinuria, and serum TBG levels have a negative correlation with urinary protein loss.

Serum TSH concentration was found to be statistically significantly higher in untreated patients than in those in the remission period of the same patients (p<0.05).

In their study to examine urinary TSH concentrations in renal disease, primary hypothyroidism and normal groups, Yoshida et al. [21] reported increased TSH excretion in the urine of

patients with nephrotic syndrome. In addition, they found that urinary TSH excretion showed a significant correlation with both urinary protein excretion and β2-microglobulin excretion.

In another study, Capri et al. [22] examined the changes in serum total and free thyroid hormones and TSH concentrations in patients with chronic nephrotic syndrome after intake of a low-protein diet.

Serum total T4 and total T3 concentrations increased significantly after diet treatment, while no significant changes were observed in mean serum fT4 and fT3 concentrations after diet. Based on these results, it is thought that the main mechanism here is the reduction in daily protein excretion in urine by giving a low-protein diet in nephrotic syndrome. In our study, similar results were obtained with the above studies, and lower TBG, T3, T4, Ft3, Ft4 and TSH levels were detected in the patient group compared to the control group.

In the literature, in a study conducted on boys with chronic renal failure at puberty [23], serum SHBG and bound testosterone levels were investigated, and serum SHBG levels were found to be significantly higher than in control children of the same age ($p<0.005$). They concluded that no significant change was detected in total testosterone level. Based on the results obtained, it is claimed that the reason for the pubertal delay in renal failure is due to changes in the testosterone fraction.

Maynar M et al [24]. in their study examining the urinary excretion of androgen hormones in professional athletes, they compared the levels of testosterone, epitestosterone, androsterone, 11-hydroxyandrosterone and SHBG after training and competition, and reported that while there was a decrease in the urinary concentrations of androgen hormones during training, they increased during the competition. These changes indicate that physical activity has an effect on the elimination of androgen hormones and the synthesis of their carrier protein, SHBG. Changes in SHBG excretion may occur even without renal pathology.

Shing et al's study of 100 patients with idiopathic nephrotic syndrome reported that hypothyroidism is common in patients with nephrotic syndrome, especially in the SRNS subgroup. Therefore, they concluded that routine screening should be performed in patients with steroid-resistant nephrotic syndrome [25].

Conclusion

In conclusion, individuals with nephrotic syndrome experience substantial alterations in serum SHBG, TBG, and the associated hormones. Based on scientific research, the probable explanation for this phenomenon is the renal loss of both hormones and hormone-binding proteins.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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